

Guidance about the effects of ibuprofen and other medications on coronavirus disease 2019 must be based on scientific evidence.

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Misguided drug advice for COVID-19

As pandemic coronavirus disease 2019 (COVID-19) continues to accelerate, the French Health Minister, Olivier Véran, has confused matters by claiming on Twitter that anti-inflammatory drugs like ibuprofen or cortisone could aggravate the infection (1). However, scientific evidence does not indicate that nonsteroidal anti-inflammatory drug (NSAID) consumption puts patients who otherwise might have mild or asymptomatic infection by severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2)—the virus that causes COVID-19—at risk of more severe disease. People taking NSAIDs for other reasons should not stop doing so for fear of increasing their COVID-19 risk.

NSAIDs work by suppressing prostaglandin synthases 1 and 2, colloquially known as COX-1 and COX-2. These enzymes produce prostaglandins (PGs), lipids that can trigger pain and fever. COX-2 produces most of the PGs relevant to pain and inflammation. NSAIDs selective for inhibiting COX-2 include celecoxib and diclofenac; ibuprofen is an NSAID that blocks both COXs. Minister Véran advised people to take paracetamol (acetaminophen) instead to treat a fever (1), but this guidance only adds to the confusion given that acetaminophen is also an NSAID (2).

We don't know with certainty whether NSAIDs could lead to more severe COVID-19 symptoms because PGs, such as PGE₂, PGD₂, and prostacyclin (PGI₂) can both promote and restrain inflammation. For example, the infection of certain immune cells (microglia) with a related coronavirus (not the one that causes COVID-19) activates a proinflammatory response (the inflammasome) to combat the pathogen; however, PGD₂ increases the expression of

PYDC3, a putative inflammasome inhibitor, in certain immune cells in mice (3). The SARS coronavirus responsible for the 2003 outbreak directly binds to the COX-2 promoter and increases its expression (4), boosting PG production capacity, and there is also evidence that PGE₂ inhibits SARS coronavirus replication (5). Indomethacin, an NSAID, blocks coronavirus RNA synthesis but independently of COX inhibition (6). By contrast, COX-2–dependent PGE₂ attenuates the chronic antiviral lymphocyte response of unresolved viral infection (7). Based on these findings, if we see a clinical signal, we can rationalize it, but therein lies the challenge. Many clinical anecdotes remain stalled in biological plausibility.

The prospect of a rapid increase in COVID-19 cases prompts us to seek covariates of disease severity, from the consumption of certain drugs before infection, to human genetic variants (8), to demographic factors such as sex and environmental exposures. In the case of NSAIDs, commonly acquired without prescription, such determination requires documentation of drug exposure and evidence of PG suppression.

Considering all of this, should patients with clinically complicated SARS-CoV-2 infections be administered NSAIDs as a treatment? No. There is no evidence of benefit. If such a patient were also to have poor kidney function, maintenance of renal blood flow becomes critically dependent on vasodilator PGs, such as PGE₂ and PGI₂ (9). Such a situation might also predispose the patient to the gastrointestinal and cardiovascular complications of NSAIDs. However, until we have robust evidence, patients in chronic pain should continue to take their NSAIDs rather than turn to opiates. Given that the elderly appear to comprise the predominant at-risk group for severe COVID-19 at this time, an association between NSAIDs and the disease may merely reflect reverse causality—that

is, infection makes you more susceptible to adverse effects of NSAIDs on the infection.

A similar rationale should be applied to evidence that coronaviruses use the angiotensin converting enzyme (ACE) 2 as a receptor for cellular entry (10). There has been speculation, but no clinical evidence, that consumption of ACE inhibitors might worsen the consequences of infection (11). Patients on ACE inhibitors should continue to take them rather than risk complications, such as stroke.

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COMPETING INTERESTS

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Permanently ban wildlife consumption

Although the origin of severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2)—the virus that causes coronavirus disease 2019 (COVID-19)—has not been identified, it is clear that China's wildlife

market played an important role in the early spread of the disease (“Mining coronavirus genomes for clues to the outbreak’s origins,” J. Cohen, News, 31 January, <https://scim.ag/COVID-19genomeclues>). On 24 February, China’s National People’s Congress adopted legislation banning the consumption of any field-harvested or captive-bred wildlife in an effort to prevent further public health threats until a revised wildlife protection law can be introduced (1). We argue that China needs to seize this opportunity and permanently ban wildlife consumption.

Since the 2003 outbreak of zoonotic SARS, China has established several management policies and regulations to control wildlife markets (2, 3). However, the vague definition of “wildlife” in the current policies and regulations results in enforcement confusion and loopholes. The current laws protect species of terrestrial and aquatic wildlife that are rare, beneficial, or economically or scientifically valuable (4), but they fail to differentiate captive-bred and wild populations. The sika deer (*Cervus nippon*), for instance, is a national, first-class protected species (5) and is also on the commercial breeding list (2). The indistinguishable differences between wild and captive populations provide opportunities for illegal bushmeat to be blended into exotic livestock and flow into the market (6).

Meanwhile, the protected species list has not been updated for nearly 30 years and covers only approximately two-thirds of the native wild species (2, 4, 5). The critically endangered spoon-billed sandpiper (*Calidris pygmaea*) (7) is still listed as a second-class protected animal (5). More than 1000 native species are absent from the protected list, including bats, which means that illegal hunting or trading of these species might not be punished and could threaten public health (4, 5).

Furthermore, penalties for illegal wildlife distribution and consumption are not sufficiently severe. Wildlife consumption is not restricted. Therefore, the demand for wildlife products remains high, with high profits and mild punishments driving the dealers (8, 9). In 2018, a man who poached about 8000 birds, including the critically endangered yellow-breasted bunting (*Emberiza aureola*) (10), was sentenced to pay only a US\$10,000 fine (11).

The Chinese legislature should revise the wildlife protection law to ensure the effectiveness of the legislation. The definition of wildlife should be clarified as distinct from captive exotic populations. Meanwhile, a more stringent management plan for exotic livestock should be established, including an individual identification system, to increase the traceability of the exotic

livestock products. The ability to technically distinguish captive from wild individuals will strengthen law enforcement. The list of protected species should be updated regularly, and all native wild species should be protected. The penalty for violating behavior should be increased, and wildlife consumption and possession should be treated as criminal offenses. Both the supply and demand sections of the wildlife trading chain should be strictly monitored and contained. China must act to permanently ban wildlife consumption in order to prevent future public health risks.

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Wildlife consumption ban is insufficient

On 24 February, China’s top legislature comprehensively prohibited the consumption of terrestrial wildlife to protect public health (1). The ban was enacted in response to the outbreak of coronavirus disease 2019 (COVID-19), which is considered to be linked to wildlife consumption (2). However, a total ban on the consumption of terrestrial wildlife alone is not enough to effectively protect public health from wildlife-associated diseases.

China’s wildlife farming industry includes 6.3 million direct practitioners and a total output value of \$18 billion (3). Curtailing this activity in a short period of time will be difficult. Conflicts may occur between the private interests of farmers and public health. It is also unclear how to dispose of the farmed animals. Killing them would be inhumane and could pose new risks to human health. Releasing them into unknown habitats in the wild could threaten ecosystem stability. Furthermore, given that banning the wildlife farming industry would threaten economic growth in many regions, implementation will be challenging.

Meanwhile, myriad traditional Chinese medicines are made from wildlife products, such as pangolin scales (4), snake bile (5), and bat feces (6), yet medicinal use of wildlife is not covered by the ban. Disease transmission risks exist during the process of hunting, storing, and transporting such wildlife for medicinal purposes, activities that will continue (6). Even if the ban could be effectively implemented, the traditional medicine industry would continue to threaten wildlife.

In addition to enacting a ban, the Chinese government should manage public health risks caused by wildlife-associated diseases by working together with wildlife protection and animal health agencies and making decisions about wildlife policies based on scientific evidence. Subsidies and financial support should be arranged to facilitate the transformation of the wildlife farming industry required by the ban, as well as made available to help transition away from the production of traditional Chinese medicine. As changes are made, the government should keep information timely and transparent so as to encourage public participation in the reform of the wildlife protection system.

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COVID-19 drives new threat to bats in China

In China, bats are traditionally symbols of good luck and happiness (1). There are more than 1400 species of bats worldwide, but more than half of them have unknown or decreasing population trends (2). Unfortunately, the suggestion that coronavirus disease 2019 (COVID-19) may have originated in bats (3) is putting them at increased risk.

As COVID-19 has spread, people in China have started requesting that hibernating bats in or near their houses be expelled (4, 5). Disturbing hibernating bats causes abnormal arousal patterns (6), which could lead to high bat mortality and potentially to the spread of other viruses. Moreover, the captured bats are being released into the wild, which is not their native habitat (4), posing further threats to their survival. These decisions are not based in fact; COVID-19 was linked to horseshoe bats (3), which do not hibernate in cities in China (7). The reputation of bats as virus carriers has even led to extreme suggestions of mass slaughter to protect public health (8). The exaggeration of bats' negative traits without regard for their positive ones could ultimately lead to their needless and intentional elimination.

Bats serve many critical roles for the ecosystem. They are biological—and economical—pesticides (9), and they contribute to the pollination and seed dispersal for many important plants (10). They are also excellent subjects for studies on healthy aging, cancer prevention, disease defense, biomimetic engineering, ecosystem functioning, and adaptive evolution (11). The need for public education about bats, including their positive and negative impacts, is urgent and vital to their conservation.

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Travel restrictions violate international law

From China's lockdown of the city of Wuhan (1) to U.S. restrictions on travelers from Europe (2) to border closures across a widening range of countries (3), governments are increasingly seeking to limit freedom of movement in response to the coronavirus disease 2019 (COVID-19). These travel restrictions have slowed, but not halted, the spread of the pandemic ("The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak," M. Chinazzi et al., Research Articles, published online 6 March, p. eaba9757). However, the necessity and benefits of this public health response are outweighed by its violation of international law. Under the International Health Regulations (2005) (IHR), binding on all World Health Organization (WHO) member states, health measures "shall not be more restrictive of international traffic and not more invasive or intrusive to persons than reasonably available alternatives" [(4), art. 43]. Given the effectiveness of community-based public health measures such as social distancing (5) and contact

tracing (6), the necessity of travel bans must be weighed against less restrictive alternatives, increased global divisions, and violated IHR obligations (7).

The IHR seeks to govern how states can come together to address collective public health threats, whereas national travel bans drive nations apart through unnecessary economic isolation and rights violations. Although the IHR demands that health measures be implemented "with full respect for the dignity, human rights, and fundamental freedoms of persons" [(4), art. 3], travel restrictions unnecessarily infringe a range of basic rights related to the freedom of movement. In the COVID-19 response, systematic social distancing interventions recommended by WHO were bypassed in the rush toward emergency travel bans, limiting individual freedoms while stoking nationalist responses.

WHO has repeatedly praised the "aggressive" measures taken by governments (8), but forced restrictions on travel undercut the global solidarity that WHO seeks in responding to this common threat. Travel bans during past outbreaks have been found to have limited public health effectiveness (9), as the prevention of disease is inextricably linked to international cooperation and rights protections (10). Rather than implementing coercive travel restrictions, governments should follow WHO recommendations in realizing transparent governance, expanding testing capacity, and implementing social distancing to protect public health. The COVID-19 pandemic will test national systems, but the world is more secure when all national responses comply with both public health necessities and global health law.

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COVID-19 has been linked to horseshoe bats, putting other bat species at risk.

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